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# THE MANAGEMENT OF METASTATIC BREAST CANCER BY HORMONE MANIPULATION*

JOSEPH H. FARROW

Attending Surgeon, Department of Surgery, Breast Service, Memorial Sloan-Kettering Cancer Center, New York; Associate Professor of Clinical Surgery, Cornell University Medical College, New York

MEDICAL literature records numerous measures that have been used locally and systemically to inhibit the progress and/or relieve the symptoms of incurable mammary cancer. Foremost among the systemic methods which have survived adequate investigation and clinical application has been the production of a hormone imbalance. This has been done by the administration of synthetic compounds, by irradiation, or by surgical removal of endocrine organs involved in the natural production of sex hormones. With such a variety of means available it is necessary to practice a selection not only of patients but of procedures, and to determine, if possible, the time at which a given modality can be used with reasonable expectation of maximum benefit and minimum risk and discomfort.

In planning treatment it is well to remember that care of the patient with incurable mammary cancer is often a long-term project. During this time there is a continuing need for maintenance of morale and

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comfort as well as the restoration of physical and functional activity.

This brings up certain fundamental problems which are controversial in nature and require individual consideration. The first deals with how much one should tell the patient regarding the prognosis and the chance of success or failure following major ablative procedures. Experience has shown that blunt predictions are frequently inaccurate, due to variations in the clinical course and duration of treated and untreated preterminal mammary cancer. Failure to recognize such limitations on accuracy has caused unnecessary mental discomfort and, in some instances, destroyed confidence in scientific medicine. It is, perhaps, best to use some degree of deception and to encourage patients to practice self-deception in discussing the nature of their illness. On the other hand, one should avoid enthusiastic speculation as to the results of treatment and certainly there is no need to impose on the willingness of the patient with incurable breast cancer to "try anything". A frank discussion with a responsible member of the family is always mandatory and will provide the basis for a better patient-physician-family understanding.

The second fundamental problem deals with timing. This concerns mainly those patients in whom the disease is limited in extent and located in areas easily accessible to irradiation. Despite the common recognition of the superiority of x-ray therapy in the local control of most primary inoperable lesions, chest wall recurrences, cutaneous, lymph node and limited skeletal metastases, there is an increasing tendency in some institutions to use systemic measures as the initial treatment for these conditions. At the Memorial Center we continue to question any advantage in the early use of hormonal alterations unless the so-called "clinically free interval" has been of short duration or the extent, inaccessibility and multiplicity of metastases prohibit adequate local therapy.

When the patient is considered suitable for treatment by hormonal manipulation, there is the problem of the best choice of the various methods. In general, this will depend upon age, physical condition, status of sex hormone activity and anatomical sites of metastases. Unfortunately, there are no precise and simple means of determining beforehand the susceptibility of a given mammary cancer to qualitative or quantitative hormonal alterations. The uncertainty of response may be reduced, however, by the use of vaginal smears for the detection and

estimation of estrogenic activity. These smears are not reliable when there is a vaginal infection or a recent history of hormone therapy or pelvic irradiation. Objective response to castration is generally considered an indication for other ablative procedures. Clinical trials of synthetic hormones are believed to be more reliable than test doses since symptomatic change is difficult to evaluate and objective improvement requires more than a few days of observation. Bio-assay and chemical analysis of excreted metabolic products are time-consuming and impractical for general use. Calcium balance studies are valuable as a sensitive index of osteolysis and as such provide means of evaluating susceptibility to hormonal alterations. There is some doubt that they furnish an equally accurate index of tumor growth since correlated changes in tumor cell population are still unproven.

Efforts to establish a relation of histologic types and grades of mammary cancer to estrogenic dependency and response to hormonal changes have, on the whole, been unsuccessful.

While it is generally agreed that the full benefits of a single method should be obtained before inaugurating another, the individual patient's needs or failure to respond to initial therapy may require either the elimination of certain procedures or the immediate combination of hormonal and nonhormonal measures.

## Criteria of Improvement

Experience has shown that it is necessary to consider symptomatic and objective improvement separately in evaluating the beneficial effects of hormonal therapy. It has been repeatedly observed that patients during and following hormonal treatment may feel better, have improved appetite and experience less pain although clinical and radiographic findings demonstrate progression of disease. Symptomatic relief and objective improvement are alike in being temporary but the former occurs more frequently. It has been noted to some degree in 65 to 75 per cent of patients treated by hormonal procedures.

Accurate assessment of the frequency and duration of remissions following hormonal manipulation is not easy in patients with incurable mammary cancer. There is the difficulty of measuring precisely the changes in size of palpable or radiographically demonstrable lesions. Further, in evaluating results it is necessary to consider multiple and variable factors besides the treatment given. Survival time and the fre-

quency and duration of objective benefit are related not only to the age and general physical condition of the patient as well as the susceptibility of the cancer to hormonal alterations but also to: 1) the extent and multiplicity of the metastases; 2) the previous biologic behavior of the cancer in rate of growth and aptitude for dissemination; 3) the natural reparative ability of the invaded tissues; and 4) the anatomic site of the metastases in relation to vital functions.

In general, objective improvement may be defined as measurable decreases in the size of soft tissue lesions and/or recalcification of osteolytic bone metastases without the appearance of new lesions. Regression of disease in some areas with concurrent progression in other sites has been observed. Such cases were considered failures regardless of symptomatic benefit. Marked symptomatic relief without progression of lesions present before treatment or the appearance of other metastases for at least six months may be considered evidence of objective improvement. On the other hand, reduction of hypercalcemia and decrease in urinary calcium excretion were not considered evidence of objective remission.

## Androgens

The accumulated experience of numerous independent observers over a period of 20 years has demonstrated the value of synthetic androgenic hormones in the treatment of advanced mammary carcinoma. Our experience, which began in 1939, at the Memorial Center has been limited largely to the use of testosterone propionate or di-hydro-testosterone, both given intramuscularly in doses of 100 mg. three times a week. Orally administered androgenic hormones with biologic potency simulating that of those administered intramuscularly have been used to a limited extent. Other compounds of an androgenic nature have been investigated but, from the observations at hand, have not proven to be of superior value in inhibiting the growth of mammary cancer.

Unless contraindicated by excessive edema from salt and water retention, hypercalcemia or obvious progress of disease, it is best to continue androgenic therapy for at least ten weeks (3,000 mg.). Treatment may be continued as long as desired when objective improvement is apparent. The undesirable virilization, particularly hirsutism, hoarseness and increased libido, which follows male hormone therapy can become quite marked and is, to some extent, related quantitatively to

dosage and duration of administration as well as individual susceptibility. On the other hand, there are certain desirable side effects, such as improved protein metabolism and increases in the red blood count. The latter may approach polycythemic levels.

Androgenic therapy is indicated in the premenopausal and early postmenopausal patients with widely disseminated disease who are unsuitable for or refuse surgical ablative procedures. It is also recommended for those patients who relapse after a remission following oophorectomy alone or combined with adrenalectomy. Androgenic hormones are of little or no value in late postmenopausal patients who do not respond to estrogenic therapy or relapse after it.

Objective improvement following male hormone therapy has been observed in 19 per cent of 133 patients with skeletal metastases, and in 22 per cent of 174 patients with soft tissue lesions. The average remission was eight months from the time objective improvement was demonstrated. Regression was maintained for six months in 68 per cent and for one year in 12 per cent of the patients showing objective improvement.

## Estrogens

Estrogenic therapy has been largely limited at the Memorial Center to patients who were approximately ten years beyond the menopause. Limited observations indicated that these compounds, if used too soon after a natural or artificial menopause, were not only without beneficial effect but in some instances may have accelerated the progress of the disease. Further, early premenopausal patients who did not initially show a favorable response to androgenic treatment or ablative procedures, or who relapsed after a remission following such treatment, have not shown a tendency to respond to estrogenic therapy.

Experience indicates that 5 mg. of di-ethyl-stilbestrol or 1 mg. of ethinyl estradiol, given orally three times a day, will produce objective improvement, particularly in soft tissue lesions and, to some extent, in osseous metastases. The frequency and duration of objective improvement are such that estrogenic therapy is perhaps the best method for controlling incurable breast cancer in elderly and feeble patients.

A few complications may occur during estrogenic therapy. Nausea and vomiting occasionally prohibit oral administration; intramuscular injections may be used in such instances. Vaginal bleeding, seldom pro-

fuse and usually due to withdrawal of the compound, may be controlled either by increasing the dose or by curettage, which is rarely necessary. Patients with limited cardiac reserve may have pulmonary and/or peripheral edema. If mild or moderate, this may be relieved by salt restriction or oral diuretics without discontinuing treatment.

Objective improvement following estrogenic therapy has been observed in 41 per cent of 111 patients with soft tissue lesions and 28 per cent of 36 patients having skeletal metastases. The average duration of remission was about eight months from the time objective improvement could be clinically demonstrated. It was six months in 61 per cent and one year in 30 per cent.

## Corticosteroids

Adrenal steroids have varied therapeutic applications. Apart from their vital need as replacement therapy following adrenalectomy or hypophysectomy, they have been used in the treatment of incurable mammary cancer. Large doses are thought to suppress adrenal activity and thereby reduce estrogenic production from this source. Corticosteroids are contraindicated when active ovarian function is present. Cortisone or, preferably, prednisone is indicated in premenopausal patients who have relapsed after or did not respond to an oophorectomy but continued to show estrogenic activity. Adrenal steroids have been used mainly in postmenopausal patients who refuse or are unsuitable for major ablative surgery.

Daily doses of 200 to 400 mg. of cortisone were initially administered orally for one week, after which the amount was reduced to 75 mg. per day. Prednisone was subsequently found to be more satisfactory than cortisone because it produces little, if any, serious electrolytic disturbances. The prednisone dose is 10 mg. 4 times a day for 3 days, then 10 mg. 3 times a day for 3 days, after which 5 mg. are given 4 times a day for maintenance.

Physiological disturbances are relatively uncommon although a few patients have developed the so-called moon-face after prolonged therapy. The principal contraindications to corticosteroid therapy are diabetes, cardiorenal insufficiency and gastroduodenal ulceration. With reference to the last, we have had the unfortunate experience of observing massive and fatal hemorrhage in a few patients who were receiving corticosteroids for either replacement or therapeutic purposes.

In an interesting study of postmortem specimens by Hartmann and Sherlock,[1] some of the bleeding gastric ulcerations were found to contain metastatic mammary cancer. They noted that metastases involving the mucosa and submucosa of the stomach and duodenum were six times more frequent in patients receiving adrenal steroids than in a control group whose survival time was of a similar duration. Soft tissue metastases, particularly lymphangiectatic pulmonary metastases, seem to respond more often than skeletal lesions, although cortisone will relieve hypercalcemia from osteolytic metastases. Objective improvement is generally less frequent and of a shorter duration than that following other hormonal procedures.

Corticosteroid therapy for uncontrolled mammary cancer has not been fully evaluated at the Memorial Center. It has been used frequently in combination with other hormonal and non-hormonal measures. Adrenal steroids used alone were most often employed as a secondary means of producing a hormonal imbalance. It is generally recognized that the frequency and duration of remissions thus produced are usually less than for the method used as the initial means of producing the hormonal change. This may partly explain why our results compared with those of others are disappointing. In an incomplete review of our observations only six (7 per cent) of 86 patients showed objective improvement. Three of the six, however, were in a subdivision of 18 patients in whom corticosteroids were used as the initial measure. The improvement rate, therefore, rises to 16 per cent of the eighteen.

## Castration

Bilateral oophorectomy is the initial surgical ablative procedure for premenopausal women with disseminated mammary cancer. It is mainly on the basis of postcastration behavior that one can estimate the dependency of a given mammary cancer on estrogenic activity. Bilateral oophorectomy is more dependable and preferable in the average patient unless there are special indications for x-ray castration. When pelvic irradiation is used, at least 2000 r. or more should be given to the midpelvic plane. Obesity would obviously contraindicate this method of sterilization.

Surgical castration alone is rarely used in the postmenopausal patient since there is no way to differentiate estrogenic activity due to residual ovarian function from that of adrenal origin. In premenopausal patients

relapse from or failure of response to androgenic therapy or pelvic irradiation does not contraindicate bilateral oophorectomy. On the other hand, poor tolerance to surgery, a fixed pelvic mass, liver metastases with jaundice, and widespread intra-abdominal metastases with ascites would contraindicate surgical castration.

Treves and Finkbeiner[2] have reported the results of surgical castrations which were done in the Memorial Center during the years 1935 through 1955. In their series of 191 patients with uncontrolled mammary cancer, objective remissions lasting three months or longer were obtained in 70 (37 per cent). There were 121 (63 per cent) failures to this procedure. One hundred forty-three of the 191 cases were having active menses and 63 (44 per cent) of these had objective regression that lasted for an average of 14 months. There were five (2.6 per cent) postoperative deaths which were due to complications from metastatic cancer in the lungs and bone rather than the operative procedure alone.

## Adrenalectomy

Huggins and Bergenstal[3] were the first to remove the adrenals for palliation of uncontrolled breast cancer on the basis that these glands provide extragonadal sources of estrogenic hormones. Bilateral adrenalectomy, following or combined with oophorectomy, is a major operation with a reported 5 per cent operative mortality that rises to 9 per cent if cases dying of disease within one month are included. Since this procedure is not curative, there should at least be selective application. Besides the usual cardiorenal and other systemic contraindications for any major surgery, the functional disturbances of vital organs from metastatic involvement must be considered. Intracranial, pulmonary and hepatic metastases with significant symptoms and clinical findings indicative of functional failure respond poorly. On the other hand, relatively asymptomatic nodular metastases in the lungs, as well as pleural metastases with fluid, do not contraindicate adrenalectomy. With the exception of liver and lymphangiectatic pulmonary metastases, soft tissue lesions and skeletal metastases show varying degrees of response.

The dependence of the mammary cancer on estrogenic stimulation, as judged by the response to androgens, castration or corticosteroids, is the most reliable indication for adrenalectomy. On the other hand,

failure to respond to these measures does not necessarily contraindicate adrenalectomy, particularly if the vaginal smears show estrogenic activity.

The technic of bilateral adrenalectomies has been described by Huggins and Dao[4] and by Randall.[5] Routine replacement therapy following operation usually requires about 25 mg. of cortisone three times a day (use cortisone and not prednisone). Excessive perspiration in hot weather may require additional salt intake and extra doses of cortisone. Sugar control in diabetics and stress from trauma, infection and additional surgery present special problems in the regulation of cortisone dosage. It is, of course, essential that the patient be cooperative and realize the dangers of acute adrenal insufficiency which will follow any sudden discontinuance of replacement therapy.

Fracchia and associates[6] have published the results of bilateral adrenalectomy following or combined with bilateral oophorectomy in 155 patients who were treated at the Memorial Center. Fourteen (9.1 per cent) died as a result of the operation or of disease within the first postoperative month. Objective response maintained for six months or longer from the date of the operation was observed in 20 (27.4 per cent) of 73 patients who had an adrenalectomy following oophorectomy. Thirty-four (41.4 per cent) of 82 patients having combined oophorectomy and adrenalectomy showed objective improvement for six months or longer. The average duration of objective remission from the time of the adrenalectomy was about 12 months.

## Hypophysectomy

In 1952, Luft and Olivecrona[7] were the first to remove the pituitary gland for the control of incurable breast cancer. The growth-inhibiting effects of hypophysectomy, either by removal or radiological destruction, have been investigated in several institutions.

It is generally believed that removal by curettement, suction and cauterization of the pituitary fossa with Zenker's solution is more complete than functional ablation by either external or interstitial irradiation. The latter, however, may be used when the surgical approach is refused or contraindicated. With a few exceptions, the indications and contraindications for hypophysectomy are essentially the same as those that apply to adrenalectomy. Severe diabetes is more easily controlled following hypophysectomy than after adrenalectomy.

The technic of hypophysectomy has been described by Ray and Pearson.[8] Like adrenalectomy, this operation is well tolerated although a majority of the patients are partly incapacitated and in poor physical condition. The most important and permanent postoperative complication is partial loss of visual fields. This occurred in 3.8 per cent of the patients reported by Pearson and Ray[9] but was serious in only two of their first series. Since the pituitary is the control center of the endocrine system, physiological disturbances requiring replacement therapy follow hypophysectomy. Besides pre- and postoperative cortisone therapy, a maintenance daily dose of 37.5 mg. is required. Thyroid deficiency usually appears within one to two months and is relieved by daily doses of 120 mg. of dessicated thyroid. Some patients develop an immediate postoperative polyuria that is usually transient. When persistent, this condition may be relieved by injection or nasal insufflation of Pitressin.

Pearson and Ray[9] have reported the results of hypophysectomy in 343 patients. All, except for nine patients in whom the procedure was done for prophylactic reasons, had uncontrolled and disseminated mammary carcinoma. Twenty-three (6.7 per cent) died as a result of the operation or within one month following surgery. Objective improvement lasting for six months or longer was noted in 113 (33 per cent) of the patients and an additional 31 (9.0 per cent) showed remissions of less than six months duration. The average duration in patients showing objective benefit for six months or longer was about eighteen months.

From the evidence at hand, little if any additional benefit can be obtained from a hypophysectomy following adrenalectomy with oophorectomy. Hence, it is generally agreed that a choice should be made between the two procedures.

Our observations support the preliminary report of the Joint Committee on Endocrine Ablative Procedures in Disseminated Mammary Carcinoma.[10] This report indicates that operative mortality, remission rates and survival times following adrenalectomy or hypophysectomy are essentially the same. We on the Breast Service at the Memorial Center favor adrenalectomy for two reasons. First, subsequent benefit has been obtained from androgenic therapy after adrenalectomy but not after hypophysectomy. Second, we believe that any worthwhile palliative measure should be readily available in both large and small hospitals.

There are more general surgeons and urologists presently qualified or in training who can do adrenalectomies than there are neurosurgeons or trainees for this limited speciality.

## Summary

In general, local procedures are initially employed when the recognized extent of the breast cancer is limited and anatomically accessible to adequate treatment. Moreover, they can easily be combined with systemic measures for better results.

With clinical material of equal prognosis and uniform methods of assessing the therapeutic results, the average frequency and duration of regression following many of the hormonal procedures are relatively the same. This suggests that the rate of tumor growth and spread is partly dependent on the complexity of an endocrine imbalance in which estrogenic activity seems to play a major role. Hence, staging provides not only a means of determining estrogenic dependency and indications for removing the various sources of estrogenic hormones but also a way for obtaining additional remissions from a general alteration of the endocrine system.

Little is known regarding the manner in which a hormonal imbalance exerts its influence on body tissues and, particularly, on mammary cancer. Failure to demonstrate any constant cytological changes which can be specifically attributed to hormonal alterations leads one to suspect that the growth-inhibiting effect may be due to a withdrawal of stimulus for tumor cell multiplication and/or stromal reactions. Not only are there varying degrees of susceptibility to hormonal alterations but, by complex inter-relationships, the endocrine system tends to replace and partly restore a normal balance. Further, the facilities of the human body for the repair of tissues and for the restoration of function by stromal reactions are limited and inconstant. Therefore, the demonstrable control of mammary cancer by hormonal alteration is uniformly temporary and largely unpredictable as to frequency and duration.

Since there are no means to determine the anatomical sites or the time in which metastases may appear from a treated or untreated breast cancer, the general policy at the Memorial Center has been to use hormonal manipulations therapeutically rather than prophylactically. This has three advantages: first, it may avoid unnecessary treatment;

second, therapy may be given more logically as needed; and third, it provides a means of staging the different methods more accurately. Even castration of the premenopausal patient with a poor postoperative prognosis is usually considered a therapeutic and not a prophylactic measure.

Adrenalectomy and hypophysectomy are major palliative operations and should be used only when the mammary cancer, although widely disseminated, does not significantly impair the function of vital organs. Other criteria for selection are not entirely adequate but patients should have a minimum life expectancy of three months and preferably six months or more. Patients with a shorter life expectancy should not be burdened with what may well be an unsuccessful major operation.

The unpredictable course of pre-terminal mammary cancer provides many pitfalls in the assessment of palliative procedures. There is a need not only for better ways to palliate but for more accurate appraisals of the methods now at hand. Finally, the management of patients with incurable mammary cancer requires knowledge, scientific interest, resourcefulness and, above all, humanity.

*REFERENCES*


1. Hartmann, W. H. and Sherlock, P. Gastroduodenal metastases from carcinoma of the breast, *Cancer 14*:426-31, 1961.
2. Treves, N. and Finkbeiner, J. A. Evaluation of therapeutic surgical castration in the treatment of metastatic, recurrent, and primary inoperable mammary carcinoma in women, *Cancer 11*:421-38, 1958.
3. Huggins, C. and Bergenstal, D. M. Inhibition of human mammary and prostatic cancers by adrenalectomy, *Cancer Res. 12*:134-41, 1952.
4. Huggins, C. and Dao, T. L.-Y. Adrenalectomy for mammary cancer: surgical technic of bilateral one-stage adrenalectomy in man, *Ann. Surg. 136*:595-603, 1952.
5. Randall, H. T. Evaluation of adrenalectomy in man: physiological changes and the effect on advanced neoplastic disease, *Bull. N. Y. Acad. Med. 30*:278-301, 1954.
6. Fracchia, A. A. and others. Results of bilateral adrenalectomy in the management of incurable breast cancer, *Cancer 12*:58-68, 1959.
7. Luft, R. and Olivecrona, H. Experiences with hypophysectomy in man, *J. Neurosurg. 10*:301-16, 1953.
8. Ray, B. S. and Pearson, O. H. Hypophysectomy in the treatment of advanced cancer of the breast. *Ann. Surg. 144*:394-403, 1956.
9. Pearson, O. H. and Ray, B. S. Hypophysectomy in the treatment of metastatic mammary cancer, *Amer. J. Surg. 99*:544-52, 1960.
10. Adrenalectomy and hypophysectomy in disseminated mammary carcinoma (Preliminary Statement by the Joint Committee on Endocrine Ablative Procedures in Disseminated Mammary Carcinoma), *J.A.M.A. 175*:787-90, 1961.